UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/351,778	07/12/99	WOLD	W 16153-7775

HM12/0824

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ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/24/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/351,778	Applicant(s) WOLD ET AL.	
	Examin r Peter Brunovskis	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *6-9,16-19,23 and 25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10-15,20-22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response filed 6/11/01 (Paper No. 15) has been entered. Amendment of claims 1, 2, 5, 10, 11, 13, 21, and 24 is acknowledged. Claims 1-27 are pending in the instant application.

Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn. Unless otherwise indicated, arguments directed to rejections rendered moot by Applicants amendments or Examiner's withdrawal will not be further addressed or acknowledged. Claims 1-5, 10-15, 20-22, and 24 are under examination in the instant application.

Claim Objections

Claim 24 is objected to because of the following informalities: In claim 24, "one or more replication-defective adenovirus which expresses an anti-cancer gene-- is grammatically incorrect. Amending the claim to --one or more replication-defective adenoviruses, each expressing an anti-cancer gene product-- would obviate the rejection. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 10-15, 20-22, and 24 are rejected or remain rejected under 35 U.S.C. 112, second paragraph, for the reasons of record and for the reasons set forth below as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 11 (and dependent claims) remain indefinite in their recitation of the phrase "or conservatively substituted variant thereof" since it is unclear what this phrase is directed to--the sequences defined by amino acids 1-26, 41-59, and 63-70, or whether the phrase is more broadly embraced by any "conservatively substituted variant" comprising substituted amino acids either within or outside the 1-26, 41-59, and 63-70 regions.

Claim 10 (and dependent claims) remains indefinite in its recitation of the term "contacting" since this terms fails to relate the process of "overexpress[ing] an adenovirus death protein" to the "method for promoting death of a neoplastic cell" which requires entry into cells, trafficking to the nucleus so as to result in expression. Applicants argue that "[t]he skilled artisan understands that adenoviruses, once placed in contact with a cell, are capable of transduction into the cell...[and that]...vector DNA...when placed in contact with the cell, is able to transfect into the cell, albeit at a lower frequency of transformation" (p. 6). This argument is not persuasive because it relies on features (i.e. transduction, transfection) not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir.

1993). Amending the claim to --comprising introducing into a neoplastic cell at least one vector-- would obviate the rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 10-15, 20-22, and 24 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office Action of 3/15/01 and for the reasons set forth below as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-5, 10-15, 20-22, and 24 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *particular* adenoviral vectors with defined structural limitations commensurate with the recited functional limitation of "replication restricted to neoplastic cells" (i.e. specific promoters in specific context etc.) and capable of killing *cultured* cells or neoplastic cells by direct intratumoral administration commensurate in scope with art recognized working examples, does not reasonably provide enablement for any and all generic vectors deemed to be "replication-restricted to neoplastic cells" or their use by any mode of administration for any type of tumor treatment. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. .

The newly amended claims (and claims dependent therefrom) recite the use of vectors that are replication-restricted to neoplastic cells. When read in light of the specification, the claimed composition and methods are directed to the use of vectors for in vivo killing of tumor cells in vivo, since there is no evidence of record for any enabling non-therapeutic use for the vectors or methods of the instant application. The definition on p. 11, line 34 through p. 12, line 8 of the specification describes "replication-restricted" as applied to a vector that replicates better in a dividing cell than in a non-dividing cell. Thus the amended claims are drawn to vectors that replicate better in neoplastic cells than in a cell of the same type that is not neoplastic and/or not dividing. However, the specification fails to provide any theoretical basis for the claimed adenoviral recombinants to replicate better in neoplastic cells that are dividing as compared to neoplastic cells that are non-dividing (e.g. cells in G_o phase). Adenoviral vectors are not dependent on cellular replication and the teachings in the specification are predicated on the use of tumor-specific promoters directing tumor specific replication which would be equally active in non-dividing tumor cells. Further, the specification fails to recite any structural limitations in the vectors that correlate with the newly recited functional limitations. The specification is primarily limited to teaching how to make and use adenoviral vectors comprising tumor-specific promoters to direct tumor cell-restricted replication, however the claims do not recite such promoters. Although there are other possible ways to make and use vectors that replicate better in neoplastic

cell than in their non-neoplastic counterparts, the specification fails to provide sufficient guidance enabling this broad scope of embodiments. For example, chimeric retroviruses with modified envelopes targeted to tumor cells essentially meet the structural limitations of the claim, however, the specification fails to provide sufficient guidance for making and using this class of vectors. Thus to the extent that the claims fail to recite distinguishing features commensurate with the level of guidance presented, the claims are not enabled.

Applicant's arguments filed 6/11/01 have been fully considered but they are only persuasive in part. The response argues that lack of enablement is not appropriately directed to the recited composition claims, since the invention has other utilities (e.g. selective destruction of cells ex vivo, transfection of plasmid into cells etc.) that are not encompassed by in vivo treatment of tumors (p. 8, first full paragraph). Given that the use of cytolytic vectors in tumor cell "purging" procedures is a relatively undeveloped art, not routinely used with any predictable level of efficacy, Applicants arguments are not persuasive with respect to this patentably distinct process. However, inasmuch as vectors are routinely used in the art to for transfecting cells to express transgenes (e.g. for experimental purposes etc.) the enablement rejection against claims 1, 3, 4, and 5 is withdrawn.

However, the rejection of claims 2 (and 11 in part) is maintained for reasons of record predicated on the undue experimentation associated with enabling the broad scope of embodiments recited in the claim(s) which lack functional (i.e. adp) activity. Applicants argue that "the skilled artisan of 1999 knows the basic structure of α-helices, transmembrane domains,

β-sheets, α/β barrels and other secondary structural motifs and functional domains (e.g. kinase domains)...[and that]...the skilled artisan is able to make simple conserved amino acid changes that have a very low likelihood of disrupting ADP function, and such changes can be made without undue experimentation" (p. 14). The response further alludes to sequence conservation relationships which provide useful data for the skilled artisan to easily make ADP functional variants.

These arguments constitute little more than unsubstantiated assertions or generalities with no clear nexus to the level of experimentation required to enable the breadth of the claimed subject matter. Importantly, the response provides no specific evidence of actual routine studies to make functional variants commensurate with the measure of scope as recited in the rejected claims. It should be noted that the secondary structural features to which Applicants allude were well known in 1976. Yet despite all the years of research since then, there is no specific evidence of record submitted to suggest that e.g. the correlation between structure and function can now be readily determined by routine experimentation (i.e. *not* "painstaking" study as described by Rudinger).

The specification does not provide sufficient guidance or expectation of success for making and using e.g. the full scope of conservatively substituted variants or those comprising other amino acids outside the 1-26, 41-59, and 63-70 regions that interfere with adp activity (i.e. in accordance with the teachings of Rudinger). The claims do not even require that the 1-26, 41-59, or 63-70 regions be in any particular configuration to one another, only that they be present.

It would require undue experimentation do determine the degree of permutations comprising these regions (and conservative variants thereof) that preserve adp activity. Absent specific evidence to the contrary, Applicants have failed to enable the broad scope of adp variant embodiments commensurate with the scope of the subject matter as claimed.

With regard to the method claims, it is noted that since claims 10 and 12 embrace methods of killing neoplastic cells in vivo, the claims are rejected for reasons of record. Amending these claims to recite cell killing methods in *cultured cells* would obviate the lack of enablement rejection against claims 10 and 12.

With regard to lack of enablement for methods for killing cells of tumors in vivo, Applicants have put forth the following arguments in an attempt to overcome the rejection:

(1) That claim 13 is not drawn to classical gene therapy, *per se*, but rather to treating a tumor with a recombinant adenoviral vector mutated to exhibit selective replication in neoplastic cells wherein the recombinant adenovirus is not designed to deliver a heterologous (non-adenoviral) gene but rather overproduce a subset of adenoviral genes (e.g. ADP) in cells under conditions not requiring heterologous gene delivery or sustained expression of ADP, in this case. Thus, the claimed method is characterized as not being subject to the same requirements of long term gene therapy, in contrast to genetic disease treatments dependent on continued expression of heterologous genes encoding e.g. CFTR etc (p. 8, second full paragraph).

(2) That the teachings of Curiel provide straightforward methods of targeting adenoviral vectors to specific types of tissues or tumor cells, supporting the use of adenoviral vectors to deliver therapeutic gene products to specific tissues, including tumors (paragr. abridging p. 8-9).

(3) That Gomez-Navarro teaches the importance of delivering optimal numbers of virions to the correct cell-type so that therapeutic gene expression is optimized and limited to that cell-type and that the instant claims are limited to vectors which are replication-restricted to cancer cells permitting a lower, non-toxic doses at the tumor site under conditions that minimize "leakage" or replication of vector into neighboring tissues thereby addressing the problems outlined by Anderson, Curiel, Gomez-Navarro, and Verma (p. 9, first full paragraph)

(4) That the specification provide adequate specific working examples of intratumoral injection on p 27, lines 31-34, p. 28, lines 25-27 and 31-32 and that the adenoviral vectors of the instant invention have been shown to be selectively active in a broad range of cultured tumor cells under conditions refractory to normal cells, thereby allowing the skilled practitioner sufficient basis for conducting simple killing assays to determine or predict therapeutic efficacy from biopsy materials (p. 9, last paragraph through p. 10, first full paragraph and p. 13, last paragraph).

Arguments (1)-(4) are not persuasive for the following reasons. First, the arguments appears to mischaracterize the problems in the art set forth in the *prima facie* case exemplified in the teachings of Anderson, Verma, Curiel, and Gomez-Navarro. For example, the references are not limited to a discussion of problems related to what Applicants characterize as "classical gene therapy" for long-term treatments against genetic defects predicated on adequate expression of

heterologous transgenes. On the other hand, the claimed methods, dependent on expression and tumor-specific replication of adenoviral vectors expressing appropriate levels of ADP under the control of a heterologous promoter essentially succumb to the same issues of expression as in any other adenoviral vector/"heterologous" transgene scenario. Moreover, claim 24 explicitly recites the use of heterologous (i.e. non-adenoviral) transgenes anyway.

The problems described in the Office Action of 3/15/01 highlight the unpredictability and undeveloped nature of the gene therapy art which apply to treatment of genetic diseases *and* cancer. Verma stated that "although more than 200 clinical trials are currently underway worldwide [including a substantial proportion for cancer], with hundreds patients enrolled, there is still no single outcome that we can point to as a success story". Further, the response puts forth unsubstantiated and unsupported assertions that adenoviral vector targeting is "straightforward" (see point 2), using a mischaracterized reliance on teachings in this highly undeveloped art that are not sufficiently described or supported in the instant application.

In spite of the fact that Applicants invention addresses some of the problems and potential solutions as outlined at the top of p. 9 in the Office Action of 3/15/01, absent working examples commensurate with the scope of the claimed subject matter, the specification is not fully enabled, particularly since the specification fails to adequately address the problems of targeting--even when presenting the methods in the context of closely compartmentalized intratumoral delivery schemes as taught by Gomez-Navarro on p. 10 of the prior Office Action. Here, the response claims that "[t]he recombinant adenoviral vector of the instant invention is able to be administered

at lower, non-toxic doses at the tumor site" (p. 9, middle paragr.). However, the response completely neglects to address the problems concerning paucity of primary receptors (i.e. CAR) on cancer as indicated by the analysis of Li et al. (i.e. p. 11 of the Office Action). These problems highlight the unpredictability and unclear expectation of success associated with the claimed methods of treatment. Nevertheless, the response maintains the position that "[t]he specification describes several modes of administration of the vector to a tumor, including direct intratumoral injection and intravenous, subcutaneous, intramuscular, transdermal, intrathecal and intracerebral injection" (p. 9, last paragr.) without any evidence or experimental support for the breadth of these different methods of administration of sufficient levels of recombinant vectors effectively home in on and specifically spread through tumor tissues even though CAR receptors appear to be more prominently expressed in non-cancerous tissues as taught by e.g. Li et al. Even if Applicants were able to render as "straightforward" the undeveloped and relatively untested re-targeting approaches described by Curiel, the instant method claims fail to recite any limitations reciting the use of adenoviral vectors capable of specifically targeting cancer cells in a CAR-independent fashion.

Regarding the appropriateness of models for testing human adenoviral anti-cancer therapies, Applicants argue that it is only necessary to test human adenoviral anti-cancer therapies on genuine human tumor models that are accepted in the art and assert that the nude mouse model is the art accepted model in the instant case (paragraph abridging p. 11-12). Applicants arguments in this regard are persuasive, particularly since no other model affords an assessment of

adenoviral-mediated cytolytic activity which does not directly depend or suffer in an obvious way in the face of a nonfunctional immune system. By amending the treatment claims to recite particular *adenoviral* recombinants in methods commensurate with the working examples, Applicants would overcome the rejection over lack of enablement.

However, it should be noted that the nude mouse models of the instant claims cannot provide a basis for evaluating incorporation of the passive immunity step which depends on a functional immune system. Importantly, the specification provides little guidance for this claimed method (i.e. cl. 14) and Applicants arguments (p. 15, first full paragraph) fails to present any evidence or experimental data (e.g. working examples) to support any measure of predictability or expectation of success for this undeveloped and unsubstantiated proposal, particularly in light of the fact that the claimed method is predicated on viral replication which would be compromised by this process.

Further, with regard to claim 24, Applicants traverse the Examiner's arguments questioning the guidance or rationale for administering a combination of replication-defective and replication-competent adenoviruses together. However, the arguments fail to address any theoretical advantage to using replication-defective adenovirus in the context of the claim which already has a replication-competent virus present. If the purpose is to promote viral spread, why not just use replication-competent adenoviruses expressing the anti-cancer gene product? If the self-limiting replication-competent vector functions to limit the replication-defective anticancer vector from overt infection of overt infection of non-neoplastic cells, as stated by Applicants, the

obvious question is why create another level of dependency, when the replication-competent vector can be engineered to express the anti-cancer gene product itself? The problem is, the specification does not provide sufficient guidance or evidence to substantiate Applicants characterization of a "well-thought out improvement over current adenoviral anticancer therapies" (p. 15). There are no working examples of this combination methodology or evidence to support a sufficiently adequate replication-competent vector-driven replication/spread of replication-defective adenovirus and expression of heterologous anticancer gene products. Given the undeveloped and unpredictable nature of the instant invention, absent sufficient guidance and a broader showing of working examples to enable the invention commensurate with the scope of the claimed subject matter, the methods can only be at best enabled for those particular methodologies reflected in the working examples on a case-by-case basis. Further, since enablement of any particular treatment methodology is highly dependent on a showing of appropriate, clinically relevant working examples, the technical issues concerning vascular permeability or barriers to spread of therapeutics to solid tissues as taught by Jain and Hobbs are somewhat academic.

The Examiner has previously included these teachings as further evidence of the unpredictability of the art for broadly enabling the methods commensurate with the scope of the claimed subject matter. The considerations of Hobbs and Jain are dependent on particular circumstances in accordance with the type of tumor and the mode of administration and require careful evaluation on a case-by-case basis. The fact that tumors *may* exhibit areas with higher

permeabilities as pointed out by Applicants (p. 10-11) cannot be extended in a general sense any more than the fact that tumor vessels in one particular subcutaneous microenvironment can be shown, under certain circumstances to reduce pore cutoff sizes to less than 7 nm (smaller than the size of adenoviruses) as taught by Hobbs. Applicants assert that the pore cutoff findings by Hobbs only refers to tumors experiencing hormone withdrawal. However, Applicants have provided no evidence to substantiate their view that regulation of tumor vessel cutoff sizes is solely regulated by hormone withdrawal. Hobbs highlights the fact that the prior art is deficient in explaining whether all tumors grown in a given site have the same pore cutoff size or are tumor-dependent, or whether pore cutoff sizes are fixed or whether they vary during tumor growth and regression (see p. 4607, top of right column). The question of pore cutoff size merely underscores the unpredictability and importance of relevant working examples that are commensurate with the claimed subject matter.

Finally, with regard to the Nature Biotechnology commentary by Fox as argued in p. 12 of the response, Applicants assert that this reference is not at appropriate citation against the instant application since it is alleged that "[t]he skilled oncologist or gene therapist recognizes that the Gelsinger death was precipitated by excessively large doses of adenovector and the alleged ignoring of clinical data showing problems with the subject during the trials" and because the instant invention is for anti-cancer therapy and involves a replication competent vector that can be administered at relatively low titers. The response further asserts that it is improper for the Office personnel to request evidence of safety in the treatment of humans. The Examiner agrees with

this view, but points out that the purpose of the commentary in Nature Biotechnology was not to make statements or inferences directed to safety and/or Applicants characterization of the so-called "media hype" (p. 11, last paragraph). Rather, the Office Action referenced Fox as further indicating the lack of reliability in delivering genes in a targeted manner in unpredictable ways wherein toxic effects can be shown to undermine the desired therapeutic effects (see p. 13 of the Office Action of 3/15/01). Since enablement of the claimed subject matter is predicated on effective targeting and a resultant therapeutic effect, the commentary of Fox is highly relevant, because they point out the unpredictability of using adenoviral vectors for gene therapy. Further, the fact that the Gelsinger trials were conducted with replication-defective viruses is of no benefit to Applicants case. First, Applicants also recite the use of replication-defective adenoviruses (cl. 24). Secondly, the use of replication-defective adenoviruses greatly underscores the *even higher* level of unpredictability when using replication competent adenoviruses, whose strict tumor-specific replication is only based on a theoretical premise. Applicants have not provided any experimental evidence to support the fact that replication of their adenoviral vectors are strictly limited to tumor tissues so as to preclude the even higher level of unpredictability associated with targeting and potential cytotoxic effects that undermine therapeutic efficacy when using replication-competent adenoviruses, given the teachings of Fox. The fact that Applicants may have had hindsight evidence to avoid the use of adenoviruses as in the case of Jesse Gelsinger is not germane to the instant case, since the outcome of those trials, however objectionable they may been, only point out the unpredictability of targeting cells and achieving the narrow windows of

efficacy as summarized by Fox. This unpredictability merely underscores the need for the claims to be limited to embodiments supported by working examples using appropriate art accepted animal models.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-4 and 10-13 remain rejected under 35 U.S.C. 102(e) as being clearly anticipated by Henderson et al. (U.S. 6,197,293, filed 3/02/98).

Applicants amendment is directed to a vector that is replication-restricted in neoplastic cells which does not read on Henderson's disclosure of adenoviral vector CN751. However, when read in the light of the full disclosure, Henderson et al. clearly anticipates the claims directed to the newly amended subject matter. Specifically, Henderson et al. discloses a recombinant vector which is replication-restricted to neoplastic cells and which overexpresses an adenovirus death protein (adp; see e.g. cl. 6). The specification further teaches to use an adp having the sequence of SEQ ID NO:6 (col. 69, SEQ ID NO:22) and further discloses methods of using the above recombinant vector for promoting death of neoplastic cells in cultured cells or tumors (see

e.g. claims 20, 32). Henderson teaches the use of vectors comprising prostate-specific response elements, including PB- or PSA-TREs operably linked to adenoviral genes essential for replication (such as E1 and/or E1B) to preferentially kill cells wherein the PB-TRE is active, such as prostate carcinoma cells or androgen receptor-producing cancer cells (see e.g. abstract and col. 18, lines 27-41). Henderson et al. further teaches that to ensure cytotoxicity further, one or more transgenes having a cytotoxic effect may also be present and under selective transcriptional control to provide higher confidence that the target cells will be destroyed, and teaches the use of ADP as a preferred embodiment (col. 18, lines 53-61). Henderson provide working examples demonstrating replication restricted to neoplastic cells (Examples 3 and 5) and further discloses a working example (Example 6, col. 48-49) of a replication competent adenoviral vector (CN751) comprising prostate-specific response elements operably linked to adp kills cells more efficiently and releases 10-40 times more virus at 48-72 hours post-infection as compared to a replication competent adenovirus lacking adp (col. 49, lines 28-34).

Applicant's arguments filed 6/11/01 have been fully considered but they are not persuasive. Applicants argue that the CN751 vector has a wild-type replication control region whose replication specificity would not be limited to neoplastic cells and that the instant claims are drawn to any and all neoplastic cells, not just prostate cells. These arguments fail to obviate the rejection, because the new grounds of rejection directed to Applicants amendment are not based on Henderson disclosure of CN751 and because Henderson's prostate cancer cell-directed teachings clearly anticipate and are embraced the broader generic embodiments of the instant

invention. Applicants are directed to claim 3 which clearly anticipates the claimed subject matter, particularly when read in light of the specification which clearly establishes the basis for both restricted replication in neoplastic cells via linkage of PB/PSA-TREs to essential adenoviral genes and further including an expression cassette comprising adp "to ensure cytotoxicity further...[and]...provide higher confidence that the target cells will be destroyed" (see e.g. col. 18, lines 53-61).

Claims 1-4 and 10-13 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Little et al. (U.S. 6,254,862, filed 3/02/98).

Little et al. discloses a recombinant vector which is replication-restricted to neoplastic cells and which overexpresses adp (see e.g. cl. 6 and col. 12, lines 47-50) The specification further teaches to use an adp having the sequence of SEQ ID NO:6 (col. 53-55, SEQ ID NO:23) and further discloses methods of using the above recombinant vector for promoting death of neoplastic cells in cultured cells or tumors (see e.g. 35, 37). Henderson teaches the use of vectors comprising alpha-fetoprotein (AFP) response elements operably linked to adenoviral genes essential for replication (such as E1 and/or E1B) to preferentially kill cells wherein the AFP is active, such as hepatocellular carcinoma- and other neoplastic cells (see e.g. abstract, col. 13, line 53 through col. 14, line 7, and col. 19, lines 31-47). Henderson et al. further teaches that to further ensure cytotoxicity, one or more transgenes having a cytotoxic effect may also be present and under selective transcriptional control to provide higher confidence that the target cells will be

destroyed, and describes the use of ADP as a preferred embodiment (col. 14, lines 10-18). Henderson provide working examples demonstrating replication restricted to neoplastic cells (Examples 3 and 4) and further discloses a working example (Example 6, columns 39-40) of a replication competent adenoviral vector (CN751) comprising prostate-specific response elements operably linked to adp kills cells more efficiently (col. 40, lines 34-36) and releases 10-40 times more virus at 48-72 hours post-infection as compared to a replication competent adenovirus lacking adp (col. 40, lines 46-53).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 10-13, and 20-22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson et al. (U.S. 6,197,293) as applied to claims 1-4 and 10-13 above in view of Freytag et al. (Hum. Gene Ther., 9:1323-1333, 6/10/98).

Claims 1-4, 10-13, and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Little et al. (U.S. 6,254,862) as applied to claims 1-4 and 10-13 above in view of Freytag et al. (Hum. Gene Ther., 9:1323-1333, 6/10/98).

Henderson et al., Little et al., and Freytag et al. have been described.

Little et al. provides an additional reference alternative to Henderson that would render as obvious the claimed invention when viewed in combination with Freytag et al. for essentially the same reasons set forth in the previous Henderson/Freytag obviousness rejection.

At the time the invention was made it would have been obvious for one of ordinary skill in the art to combine the chemotherapy/radiation combination approach of Freytag when using the replication-restricted adenoviruses of Henderson or Little, since Freytag teaches the enhanced cell killing properties when using a three-pronged approach involving additional modalities, combining a replication-competent adenovirus din conjunction with chemotherapy and radiation. Thus the invention was prima facie obvious at the time the invention was made.

Applicant's arguments filed 6/11/01 have been fully considered but they are not persuasive. Applicants assert that removal of the '293 patent as a prior art reference under 35 USC 102(e) is sufficient to remove the obviousness rejection and further submit that Freytag et al. is directed to p53 deficient cells recalcitrant to radiation therapy and that the vector in claims 20-22 is only drawn to those that are not competent to replicate in non-neoplastic cells in contrast to the Freytag's vectors which are alleged to replicate in p53-plus cells. These arguments are not persuasive in view of the fact that Applicants arguments fail to overcome the prima facie evidence for anticipation under 35 USC 102(e) for the reasons set forth above and because Applicants allegations or suggestions that Freytag's vectors are not replication-restricted to neoplastic cells is not supported by any factual evidence. However, even if Freytag's vectors were not replication-restricted to neoplastic cells as suggested by Applicants, Freytag's teachings nevertheless render

obvious the claimed invention in view of the obvious advantages of a 3-pronged cell-killing approach using a replication-competent adenoviral vector system highly analogous to that of the instant application.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO

DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632

Deborah Crouch

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